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Published:
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19 September 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/019360 A3

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING AN ADENOSINE RECEPTOR AGONIST OR ANTAGONIST

(57) Abstract: Adenosine receptor agonists, particularly an agonist which binds to the A3 adenosine receptor, are used for induction of production or secretion of G-CSF within the body, prevention or treatment of toxic side effects of a drug or prevention or treatment of leukopenia, particularly drug-induced leukopenias; and inhibition of abnormal cell growth and proliferation.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 00/00550

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K31/7052 A61K31/7076 A61K31/708 A61K31/706
A61P39/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, BIOSIS, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 50047 A (TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA) 12 November 1998 (1998-11-12) the whole document page 11, line 12 - line 35 page 12, line 15 - line 35	20-22, 29,39,46
A	---	1-19
X	WO 94 21195 A (GENSIA INC.) 29 September 1994 (1994-09-29) see the whole document, especially page 6 lines 20-25	20-22
A	---	1-8
A	WO 95 02604 A (THE UNITED STATES OF AMERICA) 26 January 1995 (1995-01-26) cited in the application see the whole document, especially page 36	1-28
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2002	14 06. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 06053 A (MEDCO RESEARCH) 11 February 1999 (1999-02-11) cited in the application page 2, line 6 - line 9	1-8
X	page 11, line 26 - line 31 page 12, line 1 - line 5 page 13, line 16 - line 19 page 15, line 6,13 see page 16 lines 11-13, 19	50-67
A	US 5 688 774 A (KENNETH A.J.) 18 November 1997 (1997-11-18) the whole document	1-8
A	SULLIVAN ET AL.: "Role of A2a adenosine receptors in inflammation" DRUG DEV. RES., vol. 45, no. 3-4, November 1998 (1998-11) - December 1998 (1998-12), pages 103-112, XP001002044 page 104, right-hand column, last paragraph page 105 page 106, left-hand column page 107, right-hand column page 108, right-hand column	1-22
A	MITTELMAN ET AL.: "Cytokines as chemotherapeutic agents" ANN. NY ACAD. SCI., vol. 255, 1975, pages 225-234, XP001004450 page 227	1,5,6, 23-30, 39,40, 43, 50-53, 56-59, 62-65
A	JACOBSON ET AL.: "Adenosine-induced cell death: evidence for receptor-mediated signalling" APOPTOSIS, vol. 4, no. 3, 1999, pages 197-211, XP001009529 page 201 -page 203 page 208, right-hand column, last paragraph page 209, left-hand column	1-28
X		50-52, 55-58, 61,64,67

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	RAMKUMAR V ET AL: "THE A3 ADENOSINE RECEPTOR IS THE UNIQUE ADENOSINE RECEPTOR WHICH FACILITATES RELEASE OF ALLERGIC MEDIATORS IN MAST CELLS" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 268, no. 23, 15 August 1993 (1993-08-15), pages 16887-16890, XP001026481 ISSN: 0021-9258 the whole document	1-8
A	SAJJADI F G ET AL: "INHIBITION OF TNF-ALPHA EXPRESSION BY ADENOSINE. ROLE OF A3 ADENOSINE RECEPTORS" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 156, 1996, pages 3435-3442, XP002916157 ISSN: 0022-1767 the whole document	1-8
A	DATABASE MEDLINE 'Online! retrieved from STN, accession no. 97307619 XP002170883 abstract & BOUMA ET AL.: "Adenosine inhibits neutrophil degranulation in activated whole blood: involvement of adenosine A2 and A3 receptors" J. IMMUNOLOGY, vol. 158, no. 11, 1 June 1997 (1997-06-01), pages 5400-5408, abstract	1-8
P,X	FISHMAN ET AL.: "A3 adenosine receptors: new targets for cancer therapy and chemoprotection" DRUG DEV. RES., vol. 50, no. 1, May 2000 (2000-05), page 101 XP001003005 abstract nr 212	1-7, 10-28, 32-38, 44,45, 49-79
P,X	FISHMAN ET AL.: "Adenosine acts as a chemoprotective agent by stimulating G-CSF production: a role for A1 and A3 adenosine receptors" J. CELL. PHYSIOL., vol. 183, no. 3, June 2000 (2000-06), pages 393-398, XP001003004 the whole document	1,2,5-7, 10,11, 13-17, 19-21, 23,24, 26-29, 31-34, 39-42, 44-46,49

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FISHMAN P ET AL: "ADENOSINE ACTS AS A CHEMOPROTECTIVE AGENT: A NEW MECHANISM" PROCEEDINGS OF THE 90TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. PHILADELPHIA, PA, APRIL 10 - 14, 1999, PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, PHILADELPHIA, PA: AACR, US, vol. 40, March 1999 (1999-03), page 677 XP001030826 the whole document	1,10,16, 20
A	---	13,14
X	KOHNO Y ET AL: "INDUCTION OF APOPTOSIS IN HL-60 HUMAN PROMYELOCYTIC LEUKEMIA CELLS BY ADENOSINE A3 RECEPTOR AGONISTS" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 219, no. 3, 27 February 1996 (1996-02-27), pages 904-910, XP001028266 ISSN: 0006-291X the whole document	50-52, 55-58, 61-64,67
X	--- YAO Y ET AL: "ADENOSINE A3 RECEPTOR AGONISTS PROTECT HL-60 AND U-937 CELLS FROM APOPTOSIS INDUCED BY A3 ANTAGONISTS" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 232, no. 2, 1997, pages 317-322, XP001035137 ISSN: 0006-291X the whole document, especially page 322 right column	50-52, 55-58, 61-64,67
X	--- JACOBSON K A ET AL: "A3 ADENOSINE RECEPTORS: PROTECTIVE VS. DAMAGING EFFECTS IDENTIFIED USING NOVEL AGONISTS AND ANTAGONISTS" DRUG DEVELOPMENT RESEARCH, NEW YORK, NY, US, vol. 45, no. 3/4, November 1998 (1998-11), pages 113-124, XP001035206 ISSN: 0272-4391	50-52, 55-58, 62-64
A	page 115 page 120, right-hand column -page 121, left-hand column	13,14
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JACOBSON K A: "Adenosine A3 receptors: novel ligands and paradoxical effects" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, GB, vol. 19, no. 5, 1 May 1998 (1998-05-01), pages 184-191, XP004121096 ISSN: 0165-6147 the whole document	20,21, 50-52, 56-58, 62-64
A		1-12
X	WO 99 02143 A (CAN FITE TECHNOLOGIES LTD ;COHN ILAN (IL); FISHMAN PNINA (IL)) 21 January 1999 (1999-01-21) cited in the application the whole document	20,22, 46,47, 62,63,66
A		1,10,13, 14,16, 29,31, 39,41, 42,50, 51,54, 56,57, 60,68,69
X	WO 99 20284 A (UNIV PENNSYLVANIA ;LIANG BRUCE T (US); NAT INST HEALTH (US); JACOB) 29 April 1999 (1999-04-29) the whole document	46,47, 62-67
X	US 5 773 423 A (GALLO-RODRIGUEZ CAROLA ET AL) 30 June 1998 (1998-06-30) cited in the application the whole document,especially column 3 lines 56-58, column 25-26, column 52 lines 29-54, examples 81 and 82	29,39, 46,47, 62-65
A	GB 2 289 218 A (MERCK & CO INC) 15 November 1995 (1995-11-15) page 1, line 20 - line 21 page 3 -page 5 page 10 -page 15 claims 2,4	50,51, 53,56, 57,59, 61-63,65

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	D'ANCONA S ET AL: "EFFECT OF DIPYRIDAMOLE, 5'-(N-ETHYL)-CARBOXAMIDOADENOSINE AND 1,3-DIPROPYL-8-(2-AMINO-4-CHLOROPHENYL)-XANTHINE ON LOVO CELL GROWTH AND MORPHOLOGY" ANTICANCER RESEARCH, HELENIC ANTICANCER INSTITUTE, ATHENS,, GR, vol. 14, no. 1A, January 1994 (1994-01), pages 93-97, XP000994765 ISSN: 0250-7005 abstract	50,51, 54-57, 60-63, 66,67
A	DUTTA S P ET AL: "SYNTHESIS AND BIOLOGICAL ACTIVITES OF SOME N-(NITRO-AMINOBENZYL) ADENOSINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 18, no. 8, 1 August 1975 (1975-08-01), pages 780-783, XP000653225 ISSN: 0022-2623 the whole document	50,51, 56,57, 62,63
A	SCHRIER D J ET AL: "THE ANTIINFLAMMATORY EFFECTS OF ADENOSINE RECEPTOR AGONISTS ON THE CARRAGEENAN-INDUCED PLEURAL INFLAMMATORY RESPONSE IN RATS" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 145, no. 6, 15 September 1990 (1990-09-15), pages 1874-1879, XP001024527 ISSN: 0022-1767 abstract page 1875, right-hand column page 1877 page 1878, right-hand column, paragraphs 2,3	1,10,12, 20
A	BONG G W ET AL: "SPINAL CORD ADENOSINE RECEPTOR SIMULATION IN RATS INHIBITS PERIPHERAL NEUTROPHIL ACCUMULATION THE ROLE OF N-METHYL-D-ASPARTATE RECEPTORS" JOURNAL OF CLINICAL INVESTIGATION, NEW YORK, NY, US, vol. 98, no. 12, 15 December 1996 (1996-12-15), pages 2779-2785, XP001035234 ISSN: 0021-9738 the whole document	1,10,20

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	MACKENZIE W M ET AL: "ADENOSINE INHIBITS THE ADHESION OF ANTI-CD3-ACTIVATED KILLER LYMPHOCYTES TO ADENOCARCINOMA CELLS THROUGH AN A3 RECEPTOR" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 54, no. 13, 1 July 1994 (1994-07-01), pages 3521-3526, XP000601409 ISSN: 0008-5472 the whole document	
A	TRITSCH G L ET AL: "SYNERGISM BETWEEN THE ANTIPROLIFERATIVE ACTIVITIES OF ARABINOSYLADENINE AND N6-BENZYLADENOSINE" CANCER BIOCHEMISTRY BIOPHYSICS, GORDON AND BREACH SCIENCE PUBLISHER, INC, US, vol. 2, no. 2, 1977, pages 87-90, XP001002040 ISSN: 0305-7232 the whole document	50,51, 54,56, 57,60
A	GUALTIERI R J ET AL: "EFFECT OF ADENINE NUCLEOTIDES ON GRANULOPOIESIS AND LITHIUM-INDUCEDGRANULOCYTOSIS IN LONG-TERM BONE MARROW CULTURES" EXPERIMENTAL HEMATOLOGY, NEW YORK, NY, US, vol. 14, August 1986 (1986-08), pages 689-695, XP001035203 ISSN: 0301-472X the whole document	1,10
A	KIM W-J ET AL: "EFFECTS OF ADENOSINE AND N6-CYCLOPENTYLADENOSINE ON SUPEROXIDE PRODUCTION, DEGRANULATION AND CALCIUM MOBILIZATION IN ACTIVATED NEUTROPHIS" DAIHAN YANGRIHAG JABJI - KOREAN JOURNAL OF PHARMACOLOGY, DAIHAN YANGRI HAGOI, SEOUL, KR, vol. 31, no. 3, 1995, pages 333-344, XP001028606 ISSN: 0377-9459 the whole document	1,10,16
P,X	SHNEYVAYS V ET AL: "INSIGHTS INTO ADENOSINE A1 AND A3 RECEPTORS FUNCTION: CARDIOTOXICITY AND CARDIOPROTECTION" DRUG DEVELOPMENT RESEARCH, NEW YORK, NY, US, vol. 50, July 2000 (2000-07), pages 324-337, XP000994767 ISSN: 0272-4391 abstract page 330 -page 331, left-hand column, paragraph 1	29,31, 39,41, 42,46

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	FISHMAN P ET AL: "ADENOSINE ACTS AS AN INHIBITOR OF LYMPHOMA CELL GROWTH: A MAJOR ROLE FOR THE A3 ADENOSINE RECEPTOR" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 36, no. 11, 2000, pages 1452-1458, XP001035229 ISSN: 0959-8049 the whole document	50-52, 56-58, 61-64
P,X	US 6 048 865 A (BARALDI PIER GIOVANNI) 11 April 2000 (2000-04-11) cited in the application page 1, line 47 - line 48 column 8, line 25 - line 26 column 7, line 52	20-22, 46,47, 50-67
P,X	WO 00 15231 A (MEDCO RES INC) 23 March 2000 (2000-03-23) page 1 -page 2 page 6, line 13 page 7, line 14 - line 22 page 8, line 16 - line 19 page 14, line 15 - line 22 page 26, line 31 page 29, line 24 - line 25 page 30 page 68 -page 74	50-53, 55-59, 61-65
P,X	WO 00 40251 A (CAN FITE TECHNOLOGIES LTD ;COHN ILAN (IL); FISHMAN PNINA (IL)) 13 July 2000 (2000-07-13)	20,22
A	the whole document	1,3,10, 12-14, 16,18
P,X	WO 00 44763 A (MACDONALD TIMOTHY ;KRON IRVING L (US); LINDEN JOEL M (US); UNIV VI) 3 August 2000 (2000-08-03)	29,31, 39,42, 43,46,47
A	page 8, line 17 - line 33 page 9 lines 17, 21-26	30,40,41
P,X	FISHMAN P ET AL: "ADENOSINE ACTS AS A CHEMOPROTECTIVE AGENT BY STIMULATING G-CSF PRODUCTION: A ROLE FOR A1&A3 ADENOSINE RECEPTORS" CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 5, no. 11, SUPPL, November 1999 (1999-11), page 3801S XP000993539 ISSN: 1078-0432 the whole document	1,2,5-7, 10,11, 13-17, 19-21

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 00/00550

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 63938 A (HILL JEFFREY L ;NYCE JONATHAN W (US); EPIGENESIS PHARMACEUTICALS I) 16 December 1999 (1999-12-16) page 9 lines 10,14,19,22,31-39 page 11, paragraph 1 page 12, last paragraph page 13, paragraph 1 page 38, paragraphs 4,5 page 45, paragraph 7 page 50 page 60; example 28 example 39 figure 7	20,22, 29,31, 39, 41-43, 46,47, 50-54, 56-60, 62-66, 76-78
A	LESCH M E ET AL: "THE EFFECTS OF (R)-N-(1-METHYL-2-PHENYLETHYL) ADENOSINE (L-PIA), A STANDARD A1-SELECTIVE ADENOSINE AGONIST ON RAT ACUTE MODELS OF INFLAMMATION AND NEUTROPHIL FUNCTION" AGENTS AND ACTIONS, BIRKHAEUSER VERLAG, BASEL, CH, vol. 34, no. 1/2, September 1991 (1991-09), pages 25-27, XP001028566 ISSN: 0065-4299 abstract page 26, left-hand column, last paragraph	1,10

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 00/00550

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23-35,50-55,68-71 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-22,29-31,39-43,46,47,50-79 (subjects 2, 3 and 6) and subject 1 : thus claims 1-79 (all partially)

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

This supplemental sheet is intended to raise objections based on the total of inventions for which (additional) fees have been paid after the notice of lack of unity of invention: i.e. it concerns inventions 1, 2, 3 and 6.

* The expressions "adenosine A3 receptor agonist", "adenosine A1 receptor agonist", "adenosine A2 receptor antagonist", "adenosine A2 receptor agonist", "a drug", "a chemotherapeutic drug" relate to compounds which are actually not well-defined and may encompass an extremely large and undefined number of different compounds. Moreover, formulas of claims 4-6 and 9 relate to an extremely large number of possible structures. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.
* The expressions " (achieving a therapeutic effect comprising) inducing G-CSF secretion or production", "inducing proliferation or differentiation of bone marrow or white blood cells", "inhibiting abnormal cell growth" are not well-defined therapeutical applications for the compounds claimed herein.
* Under the general cover of "toxic side effects of a drug", a great and unlimited number of symptoms, disorders or diseases as well as drugs can be included and it is not clear which ones are meant herein. Moreover, only one symptom (weight loss) and two drugs (cyclophosphamide and 5-fluorouracile) are sufficiently well-defined and supported by the description to allow a meaningful search to be performed (Article 6 PCT). The same objections apply to the synergetic use of combinations with "chemotherapeutic drug" for cancer therapy (only doxorubicin combinations are sufficiently supported by the description).

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Since both the compounds and the therapeutical applications are not well-defined (as mentioned above), the claims refering to said expressions or formulas are considered to lack clarity in the sense of Article 6 PCT to such an extend as to render a complete meaningful search impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, concise and supported , namely those parts concerning:

* the A3 agonists of claims 7 and 8 only in relation to the treatment of (drug-induced) myelotoxicity , (drug-induced) leukopenia (and neutropenia, blood levels of circulating leukocytes) as well as on the underlying general inventive concept (G-CSF stimulation).

* these A3 agonists in relation to cancer treatment (with or without dual effect) and (also independently) to the mixtures or interactions with 5-Fluorouracile, cyclophosphamide or doxorubicin.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

* the A3 agonists of claims 7 and 8 in relation to the treatment of drug-induced weight loss.

* the A1 agonists: CPA and CCPA mentioned on page 26 and pages 31-32 of the present description, in relation to their activity on (drug-induced) myelotoxicity, (drug-induced) leukopenia (and neutropenia, blood levels of circulating leukocytes) , as well as on the underlying general inventive concept (G-CSF stimulation).

* the A2 antagonist DPMX in combination with A3 agonists of claims 7 and 8, independently or in relation to drug-induced weight loss, as well as on the underlying general inventive concept.

* the A2 agonist DPMA in combination/interaction/synergy with the A3 agonists of claims 7 and 8, independently or in relation to cancer, as well as on the underlying general inventive concept.

CONCLUSION :
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Concerning invention number 1:
claims searched partially (incompletely): 1-28,32-38,44,45,48,49.

Concerning inventions numbers 2, 3 and 6:
claims searched partially (incompletely): 1,4,9-10,16,20,22, 29,31,39,41-43,46-47,50-54,56-79 .

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-28,32-38,44-45,48,49 (all partially)

   Use of (and pharmaceutical compositions containing) A3 adenosine receptor agonists to treat drug-induced myelotoxicity, to induce proliferation or differentiation of bone marrow or white blood cells or to prevent or treat (drug-induced) leukopenia (and neutropenia), for elevating blood levels of circulating leukocytes, possibly in combination with A1 adenosine agonists or A2 adenosine antagonists or with a drug that can cause toxic side effects (in relation to these uses).

2. Claims: 1-22 (all partially)

   Use of (and pharmaceutical compositions containing) A1 adenosine receptor agonists to treat drug-induced myelotoxicity, to induce proliferation or differentiation of bone marrow or white blood cells or to prevent or treat (drug-induced) leukopenia (and neutropenia), for elevating blood levels of circulating leukocytes, as far as not already covered by previous subject.

3. Claims: 29-31,39-43,46,47 (all partially)

   Use of (and pharmaceutical compositions containing) an A3 adenosine receptor agonist, possibly in combination with an A2 adenosine receptor antagonist or with a drug that can cause toxic side effects, to treat toxic side effects of a drug (weight loss).

4. Claims: 50-51,54,56,57,59,60,62,63,66 (all partially)

   Use of an A2 adenosine receptor agonist, alone or in combination with a chemotherapeutic/anti-tumor drug, to inhibit abnormal cell growth and compositions thereof for this use, as far as not already covered by previous inventions.

5. Claims: 23,27-28,32,36-38,48-49

   Use of (and pharmaceutical compositions containing) an A2 adenosine receptor antagonist, possibly in combination with a drug that can cause toxic side effects, to induce proliferation or differentiation of bone marrow or white blood cells or to prevent or treat (drug-induced) leukopenia (and neutropenia), for elevating blood levels of circulating leukocytes, as far as not already covered by previous invention.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. Claims: 50-79 (all partially)

Use of an A3 adenosine receptor agonist, alone or in combination with an A2 adenosine receptor agonist or with a chemotherapeutic/anti-tumor (synergetic) drug, to inhibit abnormal cell growth, in particular tumor cell growth and to treat cancer, wherein said A3R agonist may have a dual effect of both inhibiting proliferation of cancer cells and counteracting toxic side effects of a chemotherapeutic drug (and compositions thereof), as far as not already covered by previous inventions.

7. Claims: 50-51,54,56,57,59,60,62,63,66 (all partially)

Use of an A2 adenosine receptor agonist, alone or in combination with a chemotherapeutic/anti-tumor drug, to inhibit abnormal cell growth and compositions thereof for this use, as far as not already covered by previous inventions.

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